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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,623	06/06/2008	Eric Charles Reynolds	FREE-004	8524
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EXAMINER				
GRASER, JENNIFER E				
ART UNIT		PAPER NUMBER		
1645				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/596,623

Applicant(s)

REYNOLDS ET AL.

Examiner

Jennifer E. Graser

Art Unit

1645

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 and 16-19 is/are pending in the application.
- 4a) Of the above claim(s) 12-14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 16-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 June 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-946)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
- Paper No(s)/Mail Date 11/4/10, 2/24/09, 12/19/08, 10/13/08, 9/29/08
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Note: The Examiner Record of the application has changed from Patricia Duffy to Jennifer Graser.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-11 and 16-19, Species Zn²⁺, in the reply filed on 10/28/10 is acknowledged. The traversal is on the ground(s) that Reynolds (WO 99/26971) does not teach the invention. This is not found persuasive because for the reasons set forth below.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-11 and 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 and 16-19 are vague and indefinite for the recitation of "Ser(P)" in the sequences recited therein. This notation is vague and confusing and it is unclear what is meant. The claims should be amended to recite "wherein amino acid residue X of SEQ ID NO: 1 [2, etc] is a phosphoserine residue". Appropriate correction is requested.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to an antimicrobial composition comprising a divalent cation and a non-glycosylated peptide, less than about 100 amino acids, and comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: X and conservative substitutions therein. The specification fails to teach any conservative substitution that can be made in any of the recited sequences while still maintaining antimicrobial activity.

While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517). Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of

ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (amino acid substitutions), and the nature and extent of changes that can be made in these positions.

Even if an active site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. The disclosure provides no guidance as to which regions of he protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly

need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Due to the large quantity of experimentation necessary to generate the number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide the antimicrobial properties, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Additionally, the specification has demonstrated that there is synergy between the known antibacterial divalent metal cation Zn^{2+} or Ca^{2+} and kappacin, the combination which has been shown to produce a sustained antigrowth effect against an oral streptococcal biofilm. These specific results do not directly correlate to the use of any divalent cation. The specification is not enabled for the broader scope as it would take undue experimentation to discover a cation with similar results.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-11 and 16-19 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In 1999, the United States Patent and Trademark Office ("USPTO") published training materials regarding the examination of patent applications under the written description requirement of 35 U.S.C. § 112, first paragraph. (See <http://www.uspto.gov/web/offices/pac/written/sc.pdf>). Since that time, the case law and technology have developed in such a way as to necessitate a revision of the 1999 training materials. Consequently, this 2008 revision was created to supersede and replace the 1999 training materials. To the extent that any conflict exists between the 1999 training materials and the present materials, the present materials control. The claims have been evaluated with regard to written description based on the Written Description Guidelines and Training Materials published in 2008/

The instant claims are drawn to an antimicrobial composition comprising a divalent cation and a non-glycosylated peptide, less than about 100 amino acids, and comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: X and conservative substitutions therein. The specification fails to provide written description for the variants which still maintain antimicrobial activity. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification

must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicants have not described the genus of claimed polypeptides such that the specification might reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5,2001)

state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed. The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Chothia et al (THE EMBO JOURNAL, 1986, 5/4:823-26) teach that there is a limit to how much substitution can be tolerated before the original

tertiary structure is lost. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of variants of the peptides, the skilled artisan could not immediately recognize that Applicants were in possession of the claimed genus of peptides at the time of filing.

The scope of the claim includes numerous structural variants (i.e. fragments), and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification does not describe any members of the claimed genus by complete structure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the applicant was not in possession of the claimed genus. The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described.

There are no drawings or structural formulas disclosed of any of these variant structures. There is no teaching in the specification regarding which part of the structure can be varied and still produce a polypeptide which has antimicrobial activity. Although the disclosure of combined with the knowledge in the art, may put one in possession of with certain conservative substitutions, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those peptides retain antimicrobial activity. Based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that the applicant was in possession of the claimed genus of peptides based on disclosure of the single species of only the exact SEQ ID NOS: 1-11 of the peptides.

Factors to be considered in determining whether undue experimentation is required, are set forth in *In re Wands* 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to fragments and variants of polypeptides comprising SEQ ID NO: X 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed above. One of skill in the art would require guidance, in order to make or use the polypeptide compositions as instantly claimed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Reynolds et al (WO 99/26971).

Reynolds et al teach non-glycosylated peptides *comprising* SEQ ID NOs: 1-10 having less than about 100 or 70 amino acids. See sequence alignments available in Public PAIR under 'SCORE/SUPPL. Content. The composition taught by Reynolds may comprise magnesium stearate. Magnesium stearate *comprises* one magnesium divalent cation (Mg 2+) and therefore is included in the scope of the instant claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 1-11 and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds (WO 99/26971) in view of Cummins et al (J.Clin. Periodontol. 1991. 18: 455-461) and Phan et al (Oral Microbiol. 2004. Immunol. 19: 31-38).

The teachings of Reynolds are set forth above. Reynolds et al teach non-glycosylated peptides comprising SEQ ID NOs: 1-10 having less than about 100 or 70 amino acids. See sequence alignments available in Public PAIR under 'SCORE/SUPPL. Content. Reynolds teach the use of these peptides for antimicrobial compositions for treatment of caries or periodontal disease. However, Reynolds et al

does not specifically teach the use of any one of the divalent cations Zn^{2+} , Ca^{2+} , Cu^{2+} , Ni^{2+} , Co^{2+} , Fe^{2+} , Sn^{2+} , Mn^{2+} , SnF_2 , and Cu_2 in their compositions.

Cummins et al teach that the divalent metal ion zinc reduces growth and metabolism of oral bacteria by interacting with sulfhydryl groups on bacterial enzymes, inhibiting their activity. Phan et al teach that zinc is largely bacteriostatic, although very high concentrations can have a bactericidal effect. Phan teach that zinc can inhibit acid and alkali production by oral streptococci in suspensions and biofilms.

Absent evidence to the contrary, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the divalent cation, Zn^{2+} , in the compositions comprising the antimicrobial peptides taught by Reynolds because Reynolds specifically teach the use of their peptides for treatment of caries or periodontal disease and both Phan and Cummins teach the antibacterial properties of zinc against oral bacteria. The addition of zinc would be expected to increase the antimicrobial activity overall. The ratios set forth in claims 8-11 are results effective variables. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the

art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 8-11 are for any particular purpose or solve any stated problem and the prior art teaches that ingredients in pharmaceutical compositions often vary according to the particular patient and disease being treated, solutions and parameters appear to work equally as well, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the ingredients disclosed by the prior art by normal optimization procedures known in the oral bacteria art.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

2/16/11